REMARKS

Reconsideration of this application is respectfully requested.

I. Status of the Claims

With entry of this amendment, claims 32, 33, and 68-93 are pending. Claims 1-31 and 34-67 were previously cancelled.

Applicants have amended claim 80 by deleting "wherein the tetanus toxin or a fusion protein comprising a fragment C may be administered before, after, or simultaneously with the administration of a Brain Derived Neurotrophic Factor (BDNF), a Neurotrophin 4 (NT-4), or Glial-Derived Neurotrophic Factor (GDNF)."

Applicants present new claim 93. Support for this claim is found, for example, in paragraphs [013] and [0135], and Table 2 of the specification. No new matter is presented.

II. The Claims are Definite

The Office rejects claims 80-92 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Office Action, p. 2. The Office contends that "[t]he phrase 'may be administered before, after, or simultaneously' in newly added claim 80 is vague and renders the claim indefinite." *Id.*

Applicants respectfully traverse and submit that one of skill in the art would understand claim 80 to recite a method in which the recited molecules can be administered in any order. Nevertheless, solely to advance prosecution, and without acquiescing to the rejection, Applicants have amended claim 80 by deleting the phrase that begins "wherein the tetanus toxin or a fusion protein comprising a fragment C may be administered." Applicants request that the Office withdraw the rejection.

III. The Claimed Methods Are Not Obvious

The Office maintains the rejection of claims 32, 33, and 68-73, and now rejects claims 74-92, under 35 U.S.C. § 103(a) as allegedly unpatentable over Stoop *et al.*, "Synaptic modulation by neurotrophic factors: differential and synergistic effects of brain-derived neurotrophic factor and ciliary neurotrophic factor," Journal of Neuroscience 16: 3256-64 (1996) ("Stoop"), in view of Miana-Mena *et al.*, "Neuronal activity-dependent membrane traffic at the neuromuscular junction," Proc. Natl. Acad. Sci. 99: 3234-39 (2002) ("Miana-Mena") and Poo, M. "Neurotrophins as synaptic modulators," Nature Reviews 2: 24-32 (2001) ("Poo"). Office Action, p. 3.

The Office relies on the reasoning set forth in the Office Action mailed April 29, 2008. *Id.* The Office summarizes the wide variety of actions reported for neurotophic factors, and concludes:

> Since neurotrophin BDNF can increase the frequency of spontaneous synaptic currents and the amplitude of nerve-evoked synaptic current, and increase presynaptic cytosolic Ca2+ concentration, and Miana-Mena teaches that intracellular and transneuronal traffics of TTC-LacZ fusion protein strongly depend on presynaptic neural cell activity, one of ordinary skill in the art would find it obvious to use BDNF to increase neuronal transport of tetanus toxin or TTC fusion protein.

Id. at 4.

Applicants respectfully traverse and submit that the rejection fails to establish *prima facie* obviousness, because the Office has failed to demonstrate that Applicants' method was a ***predictable*** result of the asserted combination of prior art references. *See, e.g., KSR Int'l Co. v. TeleFlex Inc.*, 127 S. Ct. 1727, 1741 ("If a person of ordinary skill can implement a ***predictable*** variation, § 103 likely bars its patentability.")

(emphasis added); see also Rationales to Support Rejections Under 35 U.S.C. § 103, 72 Fed. Reg. 57526-35, (explaining that the Office is the fact-finder and requiring ***predictability*** as an element of *prima facie* obviousness).

Here, no such predictability has been shown. Indeed, the references relied on by the Office fail to show predictability in the art. In particular, those references fail to show that any of the activities reported for neurotrophins would predictably increase the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin. Moreover, the cited references do not show that it was predictable that Brain Derived Neurotrophic Factor (BDNF) would result in increased neuronal transport of the claimed tetanus toxin or a fusion protein, while, Ciliary Neurotrophic Factor (CNTF), for example, would not, as reported in Table 2 of the specification.

Applicants briefly describe the content of the references cited by the Office and how the combination of those references do not predict the results discovered by Applicants.

A. Stoop

Stoop investigated the effects of BDNF and CNTF on neuromuscular junctions in Xenopus nerve-muscle cultures. *See, e.g.*, Figure 2. As recognized by the Office, Stoop teaches that these neurotrophic factors modulate a variety of neuronal cell activities, such as the frequency of spontaneous synaptic currents, the amplitude of nerve-evoked synaptic currents, transmitter secretion, and Ca^{2+} concentrations. *See* Stoop, pp. 3261-63. Stoop teaches that "the physiological effects of these two factors are quite similar." Stoop, Discussion. Thus, Stoop teaches that BDNF and CNTF have similar effects on neuronal activity. Stoop, however, does not mention if any of the

effects of BDNF or CNTF on neuronal activity would be expected to influence neuronal transport, and if so, whether it would increase or decrease that transport. Although Stoop also reports that BDNF and CNTF's effects are mediated through different mechanisms (Discussion), Stoop provides no indication of how, or if, those different mechanisms might result in a difference in their effects on neuronal transport, as reported in the specification.

B. Poo

Poo discusses a variety of neurotrophic factors and how those factors "may participate in activity-dependent synaptic plasticity, linking synaptic activity with long-term functional and structural modification of synaptic connections." Poo, Abstract. Poo generally groups the neurotrophins together, describes them as "NTs" and uses NT to refer to the neurotrophin's supposed common activity, stating "[s]ynaptic modulation of NTs depends on a cytoplasmic signal-transduction cascade, whose efficacy may be influenced by the presence of electrical activity in the neuron." Poo, p. 28, col. 2. But even where Poo discusses individual neurotrophins, no clear picture of the expected effect of a given neurotrophin on neuronal transport emerges. For example, Poo reports that "NGF promotes synaptic transmission between cultured sympathetic neurons and cardiac myocites." Poo, p. 28, col. 1. NGF, however, does not exhibit a significant effect on neuronal transport of the tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin. Specification, p. 36, and Table 2.

Poo also discusses the evidence that BDNF may modify transmitter release. Poo, p. 28, cols. 1-2. But again, Poo does not teach whether this activity might relate to neuronal transport.

C. Miana-Mena

Miana-Mena investigated the transport of a β-galactosidase-TTC fusion protein. Miana-Mena, pp. 3235-37. Miana-Mena reported on the importance of "presynaptic activity on internalization and concentration of the fusion protein." Miana-Mena, p. 3237, col. 2. Miana-Mena came to this conclusion by studying the fusion protein in denervated neurons, and neurons treated with toxins. Miana-Mena, p. 3235, col. 1 to page 3236, col. 1. Miana-Mena does not mention any neurotrophins or attempt to correlate their activities with transport in a neuron.

D. The Office has not shown that one of skill in the art would have expected the combination of Stoop, Poo, and Miana-Mena to lead to a predictable result

The Office has focused on the alleged obviousness of the claimed method primarily in view of what Poo and Stoop teach about BDNF. But none of the cited references show that BDNF (or any other neurotrophin) would predictably lead to increased transport in a neuron.

The deficiency in the Office's assertion of *prima facie* obviousness is that none of the cited references connect the physiological effects of BDNF (or any other neurotrophin) with neuronal transport. For example, Stoop teaches that BDNF and CNTF influence the frequency of spontaneous synaptic currents, the amplitude of nerve-evoked synaptic currents, transmitter secretion, and Ca^{2+} concentrations. *See* Stoop, pp. 3261-63. Nothing in Stoop, Poo, or Miana-Mena, however, suggests that these responses have any effect on neuronal transport. Only by assuming that the skilled artisan would have concluded that BDNF and CNTF's physiological effects would

equate with increased transport could one conclude that BDNF would predictably lead to increased neuronal transport.

But that assumption fails when the prior art and specification are considered. The specification teaches that BDNF, but not CNTF, NT-3, or NGF, increases transport in a neuron. Specification, Table 2. Nothing in the combination of cited references suggests this result, and the Office has not explained how or why one of skill in the art, when viewing the similar effects of BDNF and CNTF as reported by Stoop, would have concluded that BDNF would increase transport, while CNTF would not. Accordingly, Applicants respectfully submit that the Office has failed to establish *prima facie* obviousness, and respectfully request that the Office withdraw the rejection.

IV. Priority

The Office continues to assert that the claimed subject matter "has not been disclosed by Application Nos. 09/816,467, 09/129,386, 60/055,615 and 60/065,236," and that "the effective filing date of the instant application" is September 16, 2003. Office Action, p. 5.

Applicants respectfully submit that there is no need for Applicants to address the Office's allegations because the rejections of the claims are traversed for reasons of merit. Applicants reserve the right to rely on the priorities of all the parent applications of record.

V. Conclusion

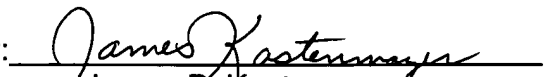
In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 16, 2009

By: 

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